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Systemic antibiotic prophylaxis for preventing infectious complications in maxillofacial trauma surgery (Protocol)

Alsharif U, Al-Moraissi E, Alabed S

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TABLE OF CONTENTS

[Intervention Protocol]

Systemic antibiotic prophylaxis for preventing infectious complications in maxillofacial trauma surgery

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of systemic antibiotic prophylaxis for preventing surgical site infections in people undergoing open reduction with or without internal fixation of trauma-induced maxillofacial fractures, and if possible to determine the most effective antibiotic type, dosage and duration.

BACKGROUND

Description of the condition

Definition

Maxillofacial fractures (MFs) are fractures of the bony structures of the midface and mandible; those include fractures of the frontal sinus, orbit, nose, zygoma, maxilla and mandible. Road traffic accidents, assaults and falls are the most common causes of MFs. Clinically, they might present with pain, bruising, swelling and numbness of surrounding tissues, nosebleeds, and facial deformities. Fractures of the mandible are often accompanied by limited and painful mouth opening and numbness of the lower lip and chin (Cienfuegos 2008; Cornelius 2009).

Epidemiology

The face is the fourth most common body region to suffer injuries, after the lower extremities, the head and the upper extremities (NTDB 2015). Due to the anatomical prominence of the nose, it is the third most common fracture in the human skeleton and the most common fractured facial bone followed by the mandible (Al-Moraissi 2015b; Hwang 2010). The incidence curve peaks in the age group 20 to 30 years especially in males. In low-income and middle-income countries, road traffic accidents and interpersonal violence are the main cause of maxillofacial fractures (Boffano 2015; Owusu 2016; Simsek 2007). In high-income countries on the other hand, there is an increasing number of MFs caused by falls in elderly people, while the number of fractures caused by assault and road traffic accidents is dropping (Atisha 2016; Boffano 2014; Martinez 2014).

Management

Radiological assessment (i.e. X-rays and CT scans) confirms the diagnosis of a fracture along with patient's history and clinical examination (Ceallaigh 2006; Ceallaigh 2007). Anatomical location, degree of fracture displacement, and soft-tissue involvement - among other factors- are important considerations when choosing the treatment method (Cornelius 2009). There are three main methods to treat a maxillofacial fracture: observation, closed reduction, and open reduction with or without internal fixation (Cienfuegos 2008; Cornelius 2009; Ellis 2006). Open reduction with internal fixation (ORIF) is the preferred method of treatment for most MFs especially displaced and comminuted fractures, as it provides superior outcomes such as higher stability and earlier mobilization of the temporomandibular joint (Al-Moraissi 2015a; Cienfuegos 2008; Cornelius 2009). Open reduction means realigning a displaced fracture through surgery, while internal fixation refers to stabilizing a fracture by using mechanical devices - usually lag screws, titanium plates or a reconstruction plate - that bridge and stabilize the fracture zone and allow healing (Cienfuegos 2008; Cornelius 2009; Ellis 2006). Nonetheless, ORIF is associated with a higher rate of postoperative complications (Villarreal 2004). Most MFs can be approached intraorally (from inside the oral cavity) but certain fractures demand an extraoral (from outside the oral cavity) approach (Ellis 1999; Toma 2003).

Complications

In general, surgical wounds are classified according to their potential risk of infectious complications into clean, clean-contaminated, contaminated and dirty wounds (Cruse 1992; Mangram 1999). Wounds from the surgical reduction of MFs can be classified as either clean-contaminated, contaminated or dirty depending on the nature of the injury (closed or open fracture), penetration of the aerodigestive tract in the surgery, and the duration between injury and the surgical treatment (Horan 1992; Mangram 1999). Following wound dehiscence, surgical site infection (SSI) is the most common complication after the open reduction of MFs (Lamphier 2003; Schaefer 2013). The US Centers for Disease Control and Prevention (CDC) set a number of clinical findings which indicate an SSI including: purulent exudate draining from the surgical site, positive microbiological culture obtained from the surgical site, at least one clinical sign of infection (pain, swelling, erythema, warmth) in a surgical site reopened by the surgeon or a diagnosis of an infection by the surgeon (Mangram 1999). Postoperative SSI rate after ORIF of a maxillofacial fracture ranges between 0% and 30% with an average of 12% (Schaefer 2013; Wladis 2013). Risk factors for postoperative SSI include open fracture, fracture site, preoperative infection, involvement of teeth in the fracture line, >72 hours delay of surgery, patient's age and comorbidities (Czerwinski 2008; Hindawi 2011; Li 2016; Seemann 2010; Soriano 2005).

Description of the intervention

Surgical antibiotic prophylaxis is defined as the administration of antibiotics to prevent SSI (Mangram 1999). There are three main regimens of administrating antibiotic prophylaxis: preoperatively, perioperatively and postoperatively. Preoperative antibiotic prophylaxis is given from time of injury up to 2 hours before surgical intervention; perioperative antibiotic prophylaxis is given immediately prior to surgical intervention and lasts during surgery, but not more than 24 hours after surgery; and postoperative antibiotic prophylaxis which lasts past the perioperative period (WHO 2016). In maxillofacial trauma surgery, prophylactic broad-spectrum antibiotics such as penicillin, cephalosporins and erythromycin are preferred unless the patient is sensitive to penicillin or if microbiological culture and sensitivity tests indicate otherwise (Zallen 1976). This practice is based on the two landmark studies by Zallen and Chole in 1975 and 1987 (Chole 1987; Zallen 1975). However, there is a lack of agreement on the most appropriate type, dose, and schedule that should be used (Zallen 1976; Kyzas 2011). The use of antibiotics is associated with allergic or toxic reactions, adverse effects and drug interactions. Long courses of antibiotics do not only put the patient at risk of adverse events, they also increase the risk of developing multidrug-resistant bacterial infections (Li 2016).

How the intervention might work

Bacterial flora of the oral and nasal cavity contaminate surgical wounds following MFs surgery which leads to high SSI rate (Zallen 1976). Additionally, the placement of titanium plates and screws in ORIF provides a suitable environment for bacteria to grow and produce their toxins. Therefore, local and regional infectious complications can be the end result (Jhass 2014; Kummer 2002; Schmidt 2000). Different antibiotics inhibit bacterial growth and multiplication through interfering with the synthesis of bacterial DNA, metabolism and cell wall structure. This prevents the adherence of bacteria to implant surface and allows the healthy immune system to overcome the infection (Hollinger 2007; Karow 2015). Thus making antibiotics the mainstay treatment of SSI. Antimicrobial prophylaxis prevent SSI by reducing the amount and virulence of microorganisms at the surgical site before, during and after an operative procedure (Mangram 1999).

Why it is important to do this review

The benefit and the most appropriate regimen of antibiotic prophylaxis in maxillofacial trauma surgery is still debated. Some studies report reduced postoperative infection rate in patients who received postoperative prophylactic antibiotics (Chole 1987; Miles 2006; Zallen 1975) while others found no evidence of protective effect (Gaal 2016; Hindawi 2011; Lovato 2009; Wladis 2013). The average length of stay in hospital after a maxillofacial fracture

ranges from 2 to 10.6 days (Boffano 2015; Pena 2014). An SSI can lead to increased hospital stay, failure of surgery and in certain cases a need for a second operation further increasing morbidity and costs (Kirkland 1999). Although a few systematic reviews attempted to determine the effects of antibiotic prophylaxis in patients suffering maxillofacial fractures (Andreasen 2006; Kyzas 2011), all of these reviews included retrospective studies and have not included several recent randomized clinical trials (RCTs). Therefore, there is a need for a systematic review including only RCTs assessing the benefits and harmful effects of antibiotic prophylaxis in maxillofacial trauma surgery, in order to provide the best evidence to clinicians.

OBJECTIVES

To assess the effects of systemic antibiotic prophylaxis for preventing surgical site infections in people undergoing open reduction with or without internal fixation of trauma-induced maxillofacial fractures, and if possible to determine the most effective antibiotic type, dosage and duration.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomized controlled trials (RCTs).

Types of participants

People of any age and gender with maxillofacial fractures (orbits, nose, zygoma, maxilla and mandible) undergoing surgical reduction of the maxillofacial fracture with or without internal fixation. We will exclude studies of non-traumatic fractures (i.e. pathological fractures). We will exclude studies that included patients treated conservatively (closed reduction).

Types of interventions

Any type of systemic antibiotic given preoperatively, perioperatively or postoperatively and administrated in any route or dose regardless of co-interventions given. Comparison can be placebo, another antibiotic, another regimen of the same antibiotic or no antibiotic prophylaxis.

Types of outcome measures

Studies reporting any the following outcomes will be eligible for inclusion if they have at least one week follow-up.

Primary outcomes

1. Postoperative infection rate, at one week, one month and three months. Any superficial or deep infection as defined by the authors or by the US Centers for Disease Control and Prevention (CDC) criteria (Mangram 1999) in or adjacent to the anatomical structures involved in the surgery will be included. If possible we will differentiate between superficial infection, deep infection that required drainage and deep infection that did not require drainage.
2. Systemic infections: defined as a SIRS (systemic inflammatory response syndrome) resulting from the postoperative surgical site infection (SSI) up to three months postsurgery.

Secondary outcomes

1. Adverse events due to the antibiotic administration.
2. Rate of retreatment surgery due to infection.
3. Length of hospital stay (LOS): defined as the number of days of hospital stay from admission to discharge.
4. Total direct and indirect costs for antibiotic treatment and postoperative infection treatment per patient.
5. Participant health-related quality of life (HRQoL): as measured using a standardized questionnaire such as EQ-5D (EuroQol 1990), Short Form SF-6 (Brazier 2002), SF-12 (Müller-Nordhorn 2004) or SF-36 (MOS I; MOS II; MOS III), or wound-specific questionnaires such as the Cardiff wound impact schedule (Price 2004).

Search methods for identification of studies

Cochrane Oral Health's Information Specialist will conduct systematic searches for randomized controlled trials and controlled clinical trials. Due to the Cochrane Embase Project to identify all clinical trials on the database and add them to CENTRAL, only recent months of the Embase database will be searched. Please see the searching page on the Cochrane Oral Health website for more information. No other restrictions will be placed on the language or date of publication when searching the electronic databases.

Electronic searches

Cochrane Oral Health's Information Specialist will search the following databases for relevant trials:

- Cochrane Oral Health's Trials Register;

- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE Ovid (from 1946 onwards);
- Embase Ovid (previous 6 months to date).

The subject strategies for databases will be modeled on the search strategy designed for MEDLINE Ovid in Appendix 1. Where appropriate, this will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomized controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, box 6.4.c (Lefebvre 2011)).

Searching other resources

The following trials registries will be searched at the Cochrane Oral Health editorial base:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://clinicaltrials.gov/);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

We will not perform a separate search for adverse effects of interventions. We will consider adverse effects described in included studies only.

Data collection and analysis

Selection of studies

Two authors (Ubai Alsharif (UA) and Essam Al-Moraissi (EAM)) will independently screen the titles and abstracts of references identified in the search. All potentially relevant articles will be selected for full-text screening. No studies will be excluded based on their language. We will utilize the Covidence platform (Covidence 2016) throughout the whole process of data collection, data extraction and while assessing the risk of bias in the included studies. We will add a study flow diagram to summarize the results of searching and selecting the studies for inclusion as recommended by the PRISMA Statement (Moher 2009).

Data extraction and management

Two authors (UA and EAM) will independently extract the data from the selected studies using a standardized form in Covidence. Any discrepancies will be discussed with the third author (Samer Alabed (SA)). We will contact study authors for clarification or missing data where necessary and feasible.

We will record the following data for each included study in the 'Characteristics of included studies' table.

- Trial design, location, number of centres, recruitment period.
- Inclusion/exclusion criteria, age and gender of participants, number randomized/analyzed, type of fracture.
- Detailed description of the intervention and comparator, including type, dosage and duration.
- Details of the outcomes reported, including method of assessment and time(s) assessed.
- Details of adverse effects, funding sources, declarations/ conflicts of interest.

Assessment of risk of bias in included studies

Based on the full text of the included studies, two authors (UA and EAM) will independently evaluate the risk of bias using the Cochrane risk of bias tool (as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)) while utilizing all the domains of the tool (random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting, and other sources of bias). Disagreements will first be discussed between the two review authors until a consensus is reached. If a consensus was not achieved a third author (SA) will act as an arbiter. The included studies will be classified as having a low, high or unclear risk of bias. We will attempt to contact the study authors to obtain missing data if insufficient information of randomization and other aspects of the trials are provided.

Measures of treatment effect

Dichotomous data

Risk ratio (RR) and its 95% confidence interval (CI) will be calculated for dichotomous data (i.e. mortality, SSI rate, adverse events, systemic infections).

Continuous data

The mean difference (MD) and its 95% CI will be calculated for LOS.

Unit of analysis issues

We will use a per-patient analysis in all our outcomes. In the case of cluster RCTs, where the results are adjusted for clustering, we will combine the adjusted measures of effects of these cluster RCTs with other RCTs using the generic inverse variance technique. If results are not adjusted for clustering, we will attempt to adjust

the results by multiplying the standard errors of the estimates by the square root of the design effect.

Dealing with missing data

Whenever possible, we will contact the original investigators to request missing data. We will try to make assumptions about the cause of the missing data and if the data were missing at random or because of a specific outcome. Where possible, we will perform an available-data analysis. We will use the methods described in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* to estimate missing standard deviations (Higgins 2011).

Assessment of heterogeneity

Statistical heterogeneity

The presence of heterogeneity will be assessed using the Chi^2 test using a significance level of 0.1. The I^2 statistic will be used to quantify inconsistency across the studies. We will interpret an I^2 greater than 50% to demonstrate high heterogeneity (see Sensitivity analysis).

Clinical heterogeneity

We will assess clinical heterogeneity by considering patients, intervention characteristics and trial settings, while methodological heterogeneity will be evaluated using the different domains of the risk of bias tool (Higgins 2011).

Assessment of reporting biases

Publication bias will be explored if there is a sufficient number of trials and reasons for any asymmetry will be considered. Funnel plot asymmetry will only be used when there are at least 10 studies included in the meta-analysis, because a funnel test with fewer studies will have too low a power to distinguish chance from real asymmetry (Section 10.4.3.1 in Higgins 2011).

Data synthesis

We will pool data in meta-analyses where they are available and it is clinically acceptable to do so, otherwise a narrative overview of the studies will be given. We will use Review Manager (RevMan) 5.3 software (RevMan 2014) to conduct meta-analyses. For the statistical analyses,our general approach will be to use a random-effects model. With this approach, the CIs for the average intervention effect will be wider than those that would be obtained using a fixed-effect approach, leading to a more conservative interpretation.

Subgroup analysis and investigation of heterogeneity

Where possible and appropriate, subgroup meta-analyses will be considered for.

1. Children (less than 18 years), and the elderly (over 65 years).
2. Studies controlled with placebo or no intervention to assess the efficacy of antibiotic prophylaxis.
3. Antibiotic types, doses and modes of administration.
4. Isolated fractures and multiple concurrent maxillofacial fractures.
5. Fracture location: mandibular fractures, orbital fractures, all other fractures (nasal, maxillary, zygoma) together. This is because the proximity to the oral cavity is an important risk factor for infection.

Sensitivity analysis

Where possible and appropriate, we will conduct sensitivity analyses on the primary outcomes to analyze the effect of including only studies at low risk of bias. If any meta-analyses include several small studies and a single very large study, we will undertake a sensitivity analysis comparing the effect estimates from both random-effects and fixed-effect models. If these are different we will report on both analyses as part of the results section, and we will consider possible interpretation.

Presentation of main results

We will use the GRADE approach, adopted by Cochrane, to interpret findings (Schunemann 2011), and we will use the GRADEprofiler GDT software (GRADEproGDT 2014) to import data from RevMan 5.3, to create the 'Summary of findings' tables. In GRADEpro, evidence relative to each specific outcome is rated as high, moderate, low and very low quality. We will start the rate of the outcomes of all randomized trials as high and downgrade them depending on: limitations in study design or execution, indirectness of evidence, unexplained heterogeneity, imprecision of results and high probability of publication bias. We will select all primary outcomes for inclusion in the 'Summary of findings' table. In addition, we will include LOS as a patient-specific outcome.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1. exp Maxillofacial injuries/
2. ((maxillofacial or nasal or facial or jaw$ or face$ or maxilla$ or mandib$ or orbital or zygoma$ or nose$ or cheek$) adj5 (fractur$ or injur$ or break$ or broken or trauma$ or surgery or surgical$)).ti,ab.
3. 1 or 2
4. anti-bacterial agents/
5. (antibacterial$ or anti-bacterial$ or antibiotic$ or anti-biotic$ or antimycobacterial$ or anti -mycobacterial$ or bacteriocid$).ti,ab.
6. exp Amoxicillin/
7. (actimoxi or amoclen or amolin or amopen or amopenixin or amox or amoxibiotic or amoxicilina or amoxicillin or amoxicilline or amoxicillinum or amoxil or amoxycillin or ampc or "apo amoxi" or augmentinxr or ax or clamoxyl or dispermox or efpenix or flemoxin or hiconcil or hydroxyampicillin or ibiamox or imacillin or larotid or moxacin or moxal or moxatag or ospamox or pamoxicillin or penamox or polymox or trimox or wymox or penicillin$).ti,ab.
8. Metronidazole/
9. (acromona or anabact or arilin or clont or danizol or deflamon or efloran or elyzol or entizol or flagyl or fossyol or ginefalvir or klion or klont or metrolyl or metronidazol or metronidazole or metronidazolum or metrotop or nalox or nidagel or noritate or novonidazol or protostat or rosadan or satric or takimetol or trichazol$ or trichex or trichopol or "tricowas b" or trikacide or trikozol or trivazol or vandazole or vertisal or zadstat).ti,ab.
10. exp Cephalosporins/
11. (ancef or cefamezin or cefazolin or cefazolina or cefazoline or cefazolinum or cephamezine or cephazolidin or cephazolin or cephazoline or cez or elzogram or kefzol or zolicef).ti,ab.
12. (ceftin or cefurax or cefuroxim or cefuroxime or cefuroximo or cefuroximum or cephuroxime or elobact or kefurox or oraxim or sharox or supacef or zinacef or "zinacef danmark" or zinnat).ti,ab.
13. Levofloxacin/
14. (cravit or elequine or floxel or iquix or "l ofloxacin" or leroxacin or levaquin or levofloxacin or levofloxacine or levofloxacino or levofloxacinum or levokacin or levox or levoxacin or mosardal or nofaxin or "ofloxacin s form" or quixin or reskuin or tavanic).ti,ab.
15. Antibiotic prophylaxis/
16. (antibiotic adj2 (prophylaxis or premedication or pre-medication)).ti,ab.
17. or/4-16
18. 3 and 17

The above search will be combined with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Lefebvre 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

CONTRIBUTIONS OF AUTHORS

Ubai Alsharif is a content expert. He drafted the methods section, edited the background section and edited the final version of the protocol. He will screen studies, extract data, conduct the statistical analysis and draft the final manuscript. This review will be a part of his doctoral thesis (Dr med. dent.) at the Johannes Gutenberg University, Mainz, Germany.

Essam Ahmed Al-Moraissi initiated and conceptualized the research question. He drafted the background section and edited the final version of the protocol. He will screen studies, extract data, assist in the statistical analysis and in drafting of the final manuscript.

Samer Alabed is an expert in the Cochrane review methodology. He edited the background and methods section of the review. He will assist in the screening and data extraction processes and function as an arbiter.

All authors approved the final version of the protocol and they will do the same with the final manuscript.

DECLARATIONS OF INTEREST

None of the authors has any conflict of interest to declare.

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